DETAILED ACTION

Receipt is acknowledged of the Remarks and Declaration filed on 03/20/08 and an IDS filed on 01/29/08. Accordingly, claims **1-7** remain pending.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Adjei et al (US 6,261,539) (provided by Applicant in the IDS filed on 01/29/08).

Adjei et al teach medicinal formulations containing a particulate drug, a propellant and a stabilizing agent comprising a water addition (see abstract and col. 2, lines 42-45). Suitable medicaments include albuterol and ipratropium bromide (see col. 2, lines 54-58). Suitable propellants include HFA 134a and HFA 227 (see col. 3, lines 32-45). Suitable stabilizer is a water addition (see col. 3, line 47-58). It is also disclosed that generally the formulation comprises about 300 ppm after and an amount of from 300 to 2000 ppm water is added as a stabilizer (col. 4, lines 8-20 and claim 7). Suitable co-solvent is ethanol (see col. 2, lines 30-33).

Claims 1-4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Jager et al (WO 9413262).

Jager et al teach stabilized medicinal aerosol solution formulations comprising medicaments that degrade or decompose by interaction with solvents or water, an HFC propellant, a cosolvent and an acid (see abstract). Most preferred medicaments for use in the said aerosol solution formulations include **ipratropium bromide and albuterol** (see page 8, lines 3-8). The suitable cosolvents include ethyl alcohol, polyethylene glycol, glycerol, etc. Most preferred cosolvent is **ethanol** (see page 9, line 17 to col. 10, line 11). The disclosed formulations contain an acid to prevent degradation. Suitable acids include ascorbic acid and **citric acid**, and the most preferred acid is citric acid (page 10, lines 17-32). Table 1 discloses a formulation comprising ipratropium bromide monohydrate, ethanol, HFA 134a, acid and water in the amount of 0.0 to 5%.

Claims 1-4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Lewis et al (EP 1219293).

Lewis et al teach a composition for use in an aerosol inhaler comprising an active agent, an HFA propellant and a cosolvent. Cosolvents include alcohols such as **ethanol** and propellants include HFA 134a and HFA 227 (see [0012] and [0010]). The active agents may be any one or more salbutamol (also known as albuterol), ipratropium bromide, beclomethasone, etc (see [0064]). The formulations may include a low volatility component such as **polyvinyl pyrolidone** (see 0056]). Other suitable low volatility materials include saturated and unsaturated carboxylic acids such as ascorbic acid (see [0055]).

Lewis also discloses the method of making the formulation and filling the aerosol inhaler. The method includes filling the container with a) one or more active materials, b) One or more low volatility components, c) One or more co-solvents followed by the addition of the HFA propellant. The formulations are said to contain up to 0.5% water and Table 2, discloses four formulations two of which contain **0.1% water**.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4 and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Ashurst et al (6,511,652).

Ashurst et al teach a metered dose inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers for dispensing an inhalation drug formulation comprising beclomethasone dipropionate, a propellant in combination with other active agents and one or more excipients (see abstract and summary). The co-solvent is preferably an alcohol such as **ethanol** (col. 2, lines 60-66). Suitable active agents include **salbutamol, ipratropium**, etc or combinations thereof. Suitable propellants include **HFA 134a or HFA 227** (col. 3, lines 5-50).

Ashurst et al also discloses that the said formulation preferably contain at least 0.015%, e.g. **0.015 to 1% water** by weight of the formulation (col. 5, lines 24-39).

Claims 1-2, 4 and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Keller et al (6,475,467).

Keller et al teach suspension formulations for delivery by metered dose inhalers comprising active agents in particulate form. It is disclosed that in such formulations the amount of **water** is less than 1% by weight (see col. 3, lines 55-67). The active agents suitable for the said formulations include ipratropium bromide, salmeterol, mometasone, etc. Formulations may comprise **two or more active agents** (col. 5, lines 20-45). Examples of preferred co-solvents include **ethanol** (col. 9, lines 1-10). Formulations may contain a buffer substance such as **citric acid** (col. 9, lines 29-35). Suitable propellants include HFA 134a and HFA 227 (col. 7, lines 54-60).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al (EP 1219293) in view of Jager et al (WO 9413262).

Lewis et al and Jager et al are discussed above. Lewis et al discloses all the components of the instant claims except for citric acid. While disclosing addition of carboxylic acids such as ascorbic acid, lacks specific disclosure on citric acid.

Jager et al teaches all the components of the formulations except for polyvinyl pyrrolidone. While disclosing various suitable cosolvents such as polyols, it does not specifically disclose polyvinyl pyrrolidone. Jager however, teaches the addition of an acid such as citric acid to the formulations as a stabilizer and a buffer.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined formulations and method of making them as taught by Lewis et al and Jager et al and end up with the claims formulations. Alternatively, it would have been obvious to one of ordinary skill in the art given the general teachings of Lewis et al on the formulations and method of making them, to have looked in the art for specific carboxylic acids such as citric acid as taught by Jager et al with the reasonable expectations of successfully preparing stable and effective formulations for aerosol administration. In other words, the claims would have been obvious because a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **1-7** are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,423,298 in view of Lewis et al (EP 1219293). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant Application would have been obvious over the claims of the U.S. Patent '298 in view of Lewis et al '293. Specifically, the instant claims and the reference claims are drawn to a formulation comprising an HFA propellant, one or more active agents and one or more excipients. The instant claims additionally require 0.13 to 0.18% water and reference claims do not require water. Lewis et al discloses similar formulations and teaches that the amount of water preferably is about 0.1%. It would have been obvious to one of ordinary skill in the

art to have implemented the teachings of 0.1% water of Lewis et al in the formulations of the reference claims with a reasonable success.

Response to Arguments

Applicant's arguments filed 03/20/08 have been fully considered but they are not persuasive.

Applicants main argument appears to be that none of the references applied in the rejection of claims 1-7 teach the specific water concentration range of 0.13 to 0.18%. Applicant then concludes that none of the references can properly anticipate the narrow range of the instant claims. The arguments are combined with a Declaration by George Destefano. The Declaration provides data obtained form various experiments done on albuterol sulfate and ipratropium bromide. Each experiment comprises a different amount of water. In concluding Mr. Destefano argues that the data shows that formulations comprising 1500 ppm or greater (equivalent to 0.15%) water is needed to ensure that the single actuation reproducibility difference does not impact the product. In other words, water content of less than 1200 ppm resulted in poor reproducibility, while water content of 1500 to 2500 ppm (equivalent to 0.15 to 0.25%) exhibited good results (see Declaration, page 2). This is not persuasive, because the data provided does not fully support applicants assertion. For better illustration, we can look at three tables, each showing a different water content. Table for AS No. 02-10-7501 has a water content of much lower than 1500 ppm. At 25 actuation, Can 1, the number for albuterol is 115.13 and for ipratropium it is 20.56. The same numbers for a water

content of 2500 ppm (AS No. 02-10-7506), are 118.31 and 20.22 respectively. The same numbers for a water content of 3500 ppm (AS No. 02-10-7508) are 119.26 and 21.31. There is no significant difference between, for example, 115.13, 118.31 and 119.26 (for albuterol). There is even less distinction shown between 20.56, 20.22 and 21.31 (for ipratropium).

Thus it is the Examiner's position that no unexpected results shown and that references teaching a water content the overlaps the cited ranges anticipates the claim ranges.

Claims 1-7 remain rejected.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 03/20/08 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINA HAGHIGHATIAN whose telephone number is (571)272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mina Haghighatian/

Primary Examiner
Art Unit 1616